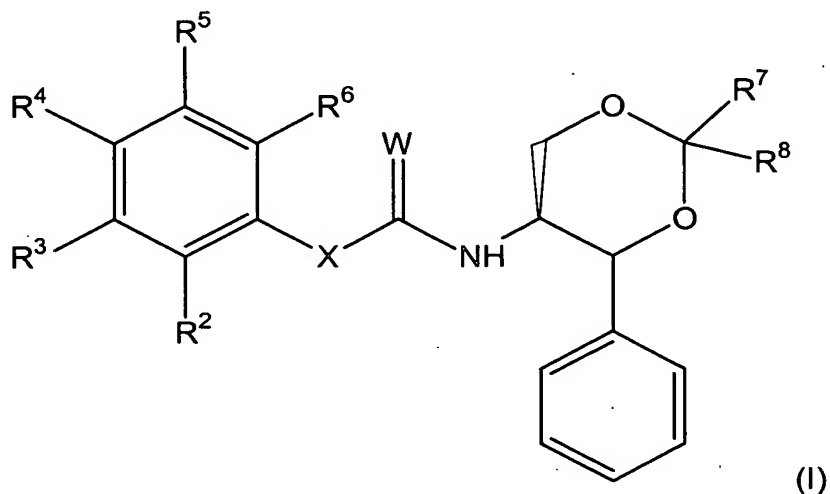


CLAIMS

What is claimed is:

- 5 1. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound of formula (I):



wherein:

- 10 R^2 is H, F, Cl, Br, I, cyano, nitro, COR^a , $COOR^a$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, phenyl, C_{2-9} heterocyclyl, (phenyl)- C_{1-6} alkylene, (C_{2-9} heterocyclyl)- C_{1-6} alkylene, or (C_{3-7} cycloalkyl)- C_{1-6} alkylene; wherein R^a is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or (C_{3-7} cycloalkyl)- C_{1-6} alkylene;
- 15 R^3 is H, F, Cl, Br, I, cyano, hydroxy, nitro, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, phenyl, C_{2-9} heterocyclyl, (phenyl)- C_{1-6} alkylene, (C_{2-9} heterocyclyl)- C_{1-6} alkylene, or (C_{3-7} cycloalkyl)- C_{1-6} alkylene
- or R^2 and R^3 taken together with the phenyl ring to which they are attached
- 20 form a naphthyl;
- R^4 is H, F, Cl, Br, I, cyano, hydroxy, nitro, amino, COR^b , $COOR^b$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, phenyl, C_{2-9} heterocyclyl, (phenyl)- C_{1-6} alkylene, (C_{2-9} heterocyclyl)- C_{1-6} alkylene, or

- (C₃₋₇ cycloalkyl)-C₁₋₆ alkylene; wherein R^b is H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or (C₃₋₇ cycloalkyl)-C₁₋₆ alkylene;
- R⁵ is H, F, Cl, Br, I, cyano, hydroxy, nitro, amino, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, or C₃₋₇ cycloalkyl;
- 5 R⁶ is H, F, Cl, Br, I, cyano, hydroxy, nitro, amino, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, phenyl, C₂₋₉ heterocyclyl, (phenyl)-C₁₋₆ alkylene, (C₂₋₉ heterocyclyl)-C₁₋₆ alkylene, or (C₃₋₇ cycloalkyl)-C₁₋₆ alkylene;
- X is NH, O, or CH₂;
- 10 W is S, O, or =N-CN;
- each of R⁷ and R⁸ is independently selected from H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, (C₃₋₇ cycloalkyl)-C₁₋₆ alkylene, phenyl, and (phenyl)-C₁₋₆ alkylene, provided at least one of R⁷ and R⁸ is not H;
- wherein each of the above hydrocarbyl or heterocarbyl moieties can be
- 15 optionally substituted with between 1 and 3 substituents selected from F, Cl, Br, I, cyano, hydroxy, nitro, amino, COR^c, COOR^c, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkylthio, C₁₋₃ haloalkyl, and C₃₋₆ cycloalkyl; wherein R^c is H or C₁₋₆ alkyl;
- provided when W is O, X is NH, and R⁷ and R⁸ are each methyl, and R³, R⁴,
- 20 R⁵, and R⁶ are each H, then R² is not H, 2-chlorophenyl, or 3-quinolinyl; and pharmaceutically acceptable salts, esters, amides, and hydrates thereof.
2. A composition of claim 1, wherein W is O.
- 25 3. A composition of claim 1, wherein R² and R⁴ are not hydrogen.
4. A composition of claim 1, wherein X is CH₂.
5. A composition of claim 1, wherein X is NH.
- 30 6. A composition of claim 1, wherein each of R⁷ and R⁸ is independently selected from methyl, ethyl, and propyl.

7. A composition of claim 1, wherein at least two of R^3 , R^5 , and R^6 are H.
8. A composition of claim 1, wherein R^2 is H, Cl, Br, I, methyl, halomethyl, cyano, amino, C₂₋₉ heterocyclyl, phenyl, or phenyl substituted with hydroxy, thiol, nitro, cyano, or halo.
9. A composition of claim 8, wherein R^2 is Cl, Br, I, methyl, cyano, C₂₋₉ heteroaryl, phenyl, or phenyl substituted with hydroxy, thiol, or halo.
10. A composition of claim 1, wherein R^3 is H or methyl.
11. A composition of claim 10, wherein R^3 is H.
12. A composition of claim 1, wherein R^4 is H, Cl, Br, I, methyl, halomethyl, cyano, amino, C₂₋₉ heterocyclyl, phenyl, or phenyl substituted with hydroxy, thiol, nitro, cyano, or halo.
13. A composition of claim 12, wherein R^4 is H, Cl, Br, I, or methyl.
14. A composition of claim 1, wherein R^5 is H, Cl, Br, I, methyl, halomethyl, methoxy, thiomethyl, ethyl, ethoxy, or thioethyl.
15. A composition of claim 14, wherein R^5 is H, methyl, or Cl.
16. A composition of claim 1, wherein the stereochemistry of the two dioxane chiral centers is (S,S).
17. A composition of claim 1, wherein said compound of formula (I) is selected from: 1-(2-Bromo-phenyl)-3-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea; 1-Biphenyl-2-yl-3-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea; and 1-(2,3-Dichloro-phenyl)-3-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea.

18. A composition of claim 1, wherein said compound of formula (I) is selected from: 1-(4-Bromo-2-chloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
 1-(2,4-Dibromo-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
 1-(2,4-Dichloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
 1-(2-Chloro-5-methyl-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-thiophen-2-yl-phenyl)-urea;
 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-iodo-phenyl)-urea;
 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(4-iodo-phenyl)-urea;
 1-(4-Bromo-2-methyl-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
 1-(2-Bromo-4-methyl-phenyl)-3-((4S, 5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
 1-(2-Cyano-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
 1-(3'-Chloro-biphenyl-2-yl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
 1-(2,5-Dimethyl-phenyl)-3-((4S, 5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea; and
 1-Biphenyl-2-yl-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea.
19. A composition of claim 1, wherein said compound of formula (I) is selected from: 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-trifluoromethyl-phenyl)-urea;
 1-(4-Bromo-3-methyl-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;

- 1-(2-Bromo-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
- 1-(2,5-Dichloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)- urea;
- 5 1-(2-Chloro-5-trifluoromethyl-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
- 1-(2-Bromo-phenyl)-3-((4R,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea; and
- 10 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-thiophen-3-yl-phenyl)-urea.
20. A composition of claim 1, wherein said compound of formula (I) is selected from: 1-(2,4-Dimethyl-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
- 15 1-(2-Chloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
- 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-fluoro-phenyl)-urea;
- 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-o-tolyl-urea;
- 20 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-nitro-phenyl)-urea;
- 2-(2-Bromo-phenyl)-N-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-acetamide;
- ((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-carbamic acid 2-chloro-phenyl ester;
- 25 1-(4-Bromo-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
- 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-methoxy-phenyl)-urea;
- 30 1-(4-Chloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
- 2-[3-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-ureido]-benzoic acid;

2-[3-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-ureido]-benzoic acid methyl ester;

1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-isopropyl-phenyl)-urea;

5 1-(2,6-Dichloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;

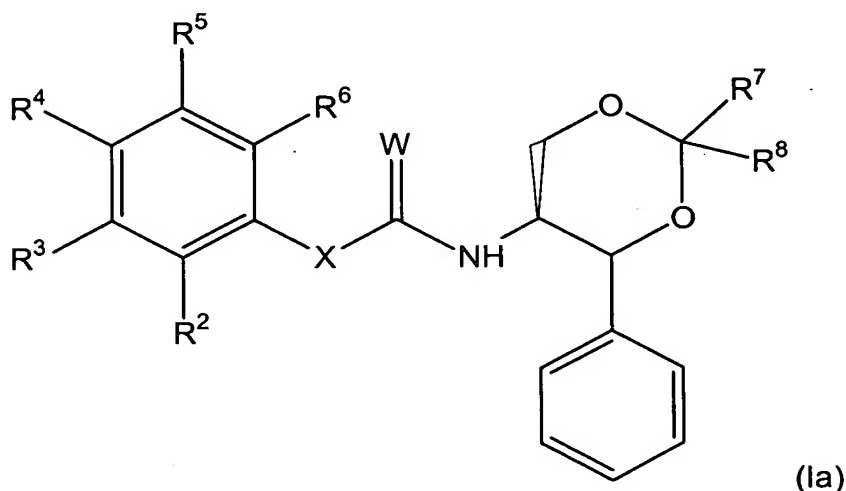
1-(3-Bromo-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;

10 1-(2,4-Difluoro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea; and

1-(3-Chloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea.

21. A compound of formula (Ia):

15



wherein:

20 R^2 is H, F, Cl, Br, I, cyano, nitro, COR^a , $COOR^a$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, phenyl, C_{2-9} heterocyclyl, (phenyl)- C_{1-6} alkylene, (C_{2-9} heterocyclyl)- C_{1-6} alkylene, or (C_{3-7} cycloalkyl)- C_{1-6} alkylene; wherein R^a is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or (C_{3-7} cycloalkyl)- C_{1-6} alkylene;

R^3 is H, F, Cl, Br, I, cyano, hydroxy, nitro, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, phenyl, C_{2-9} heterocyclyl,

(phenyl)-C₁₋₆ alkylene, (C₂₋₉ heterocyclyl)-C₁₋₆ alkylene, or (C₃₋₇ cycloalkyl)-C₁₋₆ alkylene

or R² and R³ taken together with the phenyl ring to which they are attached form a naphthyl;

5 R⁴ is H, F, Cl, Br, I, cyano, hydroxy, nitro, amino, COR^b, COOR^b, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, phenyl, C₂₋₉ heterocyclyl, (phenyl)-C₁₋₆ alkylene, (C₂₋₉ heterocyclyl)-C₁₋₆ alkylene, or (C₃₋₇ cycloalkyl)-C₁₋₆ alkylene; wherein R^b is H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or (C₃₋₇ cycloalkyl)-C₁₋₆ alkylene;

10 R⁵ is H, F, Cl, Br, I, cyano, hydroxy, nitro, amino, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, or C₃₋₇ cycloalkyl;

R⁶ is H, F, Cl, Br, I, cyano, hydroxy, nitro, amino, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, phenyl, C₂₋₉ heterocyclyl, (phenyl)-C₁₋₆ alkylene, (C₂₋₉ heterocyclyl)-C₁₋₆ alkylene, or (C₃₋₇ cycloalkyl)-C₁₋₆ alkylene;

15 X is NH, O, or CH₂;

W is S, O, or =N-CN;

each of R⁷ and R⁸ is independently selected from H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, (C₃₋₇ cycloalkyl)-C₁₋₆ alkylene, phenyl, and (phenyl)-C₁₋₆ alkylene,

20 provided at least one of R⁷ and R⁸ is not H;

wherein each of the above hydrocarbonyl or heterocarbonyl moieties can be optionally substituted with between 1 and 3 substituents selected from F, Cl, Br, I, cyano, hydroxy, nitro, amino, COR^c, COOR^c, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkylthio, C₁₋₃ haloalkyl, and C₃₋₆ cycloalkyl; wherein R^c is H or C₁₋₆ alkyl;

25 provided when W is O, X is NH, and R⁷ and R⁸ are each methyl, and R³, R⁴, R⁵, and R⁶ are each H, then R² is not H, Br, phenyl, 2-chlorophenyl, or 3-quinoliny;

provided when W is O, X is NH, and R⁷ and R⁸ are each methyl, and R⁴, R⁵, and R⁶ are each H, then R³ is not Cl nor is R³ taken together with R²;

30 and
provided when W is O, X is NH, and R⁷ and R⁸ are each methyl, and R², R⁵, and R⁶ are each H, then R⁴ is not Cl;

and pharmaceutically acceptable salts, esters, amides, and hydrates thereof.

22. A compound of claim 21, wherein W is O.
- 5 23. A compound of claim 21, wherein R² and R⁴ are not hydrogen.
24. A compound of claim 21, wherein X is CH₂.
25. A compound of claim 21, wherein X is NH.
- 10 26. A compound of claim 21, wherein each of R⁷ and R⁸ is independently selected from methyl, ethyl, and propyl.
27. A compound of claim 21, wherein at least two of R³, R⁵, and R⁶ are H.
- 15 28. A compound of claim 21, wherein R² is H, Cl, Br, I, methyl, halomethyl, cyano, amino, C₂₋₉ heterocyclyl, phenyl, or phenyl substituted with hydroxy, thiol, nitro, cyano, or halo.
- 20 29. A compound of claim 28, wherein R² is Cl, Br, I, methyl, cyano, C₂₋₉ heteroaryl, phenyl, or phenyl substituted with hydroxy, thiol, or halo.
30. A compound of claim 21, wherein R³ is H or methyl.
- 25 31. A compound of claim 30, wherein R³ is H.
32. A compound of claim 21, wherein R⁴ is H, Cl, Br, I, methyl, halomethyl, cyano, amino, C₂₋₉ heterocyclyl, phenyl, or phenyl substituted with hydroxy, thiol, nitro, cyano, or halo.
- 30 33. A compound of claim 32, wherein R⁴ is H, Cl, Br, I, or methyl.

34. A compound of claim 21, wherein R⁵ is H, Cl, Br, I, methyl, halomethyl, methoxy, thiomethyl, ethyl, ethoxy, or thioethyl.
35. A compound of claim 34, wherein R⁵ is H, methyl, or Cl.
36. A compound of claim 21, wherein the stereochemistry of the two chiral centers is (S,S).
37. A compound of claim 21, wherein said compound of formula (Ia) is selected from: 1-(4-Bromo-2-chloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
1-(2,4-Dibromo-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
1-(2,4-Dichloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
1-(2-Chloro-5-methyl-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-thiophen-2-yl-phenyl)-urea;
1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-iodo-phenyl)-urea;
1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(4-iodo-phenyl)-urea;
1-(4-Bromo-2-methyl-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
1-(2-Bromo-4-methyl-phenyl)-3-((4S, 5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
1-(2-Cyano-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
1-(3'-Chloro-biphenyl-2-yl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea; and
1-(2,5-Dimethyl-phenyl)-3-((4S, 5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea.

38. A compound of claim 21, wherein said compound of formula (Ia) is selected from: 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-trifluoromethyl-phenyl)-urea;
- 5 1-(4-Bromo-3-methyl-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)- urea;
- 1-(2,5-Dichloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)- urea;
- 10 1-(2-Chloro-5-trifluoromethyl-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea; and
- 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-thiophen-3-yl-phenyl)-urea.
39. A compound of claim 21, wherein said compound of formula (Ia) is selected from: 1-(2,4-Dimethyl-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
- 15 1-(2-Chloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
- 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-fluoro-phenyl)-urea;
- 20 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-o-tolyl-urea;
- 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-nitro-phenyl)-urea;
- 25 2-(2-Bromo-phenyl)-N-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-acetamide;
- ((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-carbamic acid 2-chloro-phenyl ester;
- 1-(4-Bromo-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;
- 30 1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-methoxy-phenyl)-urea;
- 2-[3-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-ureido]-benzoic acid;

2-[3-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-ureido]-benzoic acid methyl ester;

1-((4S,5S)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(2-isopropyl-phenyl)-urea;

5 1-(2,6-Dichloro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea;

1-(3-Bromo-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea; and

10 1-(2,4-Difluoro-phenyl)-3-((4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-urea.

40. A method for treating obesity, said method comprising administering to a subject a pharmaceutically-effective amount of a pharmaceutical composition of claim 1.

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41. A method for treating a sleep/wake disorder, said method comprising administering to a subject a pharmaceutically-effective amount of a pharmaceutical composition of claim 1.

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42. A method of claim 41, wherein said sleep/wake disorder is selected from insomnia, narcolepsy, jet lag, and sleep apnea.

43. A method for treating a disease or condition mediated by an orexin-2 receptor, said method comprising administering to a subject a pharmaceutically-effective amount of a pharmaceutical composition of claim 1.

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44. A method for inhibiting an orexin-2 receptor, said method comprising contacting said receptor with a compound of claim 1.

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45. A method of claim 44, wherein said orexin-2 receptor is human.

- 46. A method of claim 44, wherein said compound is selective for orexin-2 receptor over orexin-1 receptor by a factor of at least 10.
- 47. A method of claim 46, wherein said factor is at least 100.

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